Zinc lozenges and vitamin C for the common cold are not examples of placebo effect in action

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In the introduction to their paper on the reporting of blinding in trial publications, Bello et al. [1] write that compromised blinding has raised concerns and, as examples, refer to studies on zinc lozenges and vitamin C for the common cold [2-4].

In 1975, Karlowski et al. [2] concluded from their vitamin C and common cold trial that “the effects [of ascorbic acid] demonstrated might be explained equally well by a break in the double blind”. The placebo consisted of lactose, which is easily distinguishable from ascorbic acid by taste. Statisticians and clinical trialists have frequently cited the Karlowski study in textbooks, the CONSORT statement [5], and other publications as an example of the placebo effect in action. In 1996, however, I showed in this journal that the Karlowski report contained erroneous analysis [6]. For example, 42% of the common cold episodes were missing from the comparison of the “blinded” vs. “unblinded” participants even though Karlowski presented those two groups as if they were complementary. Karlowski's placebo-effect explanation also contains several other problems [6,7]. Over two dozen trials with valid placebos, such as citric acid, have clearly shown that the effects of vitamin C on the common cold are not placebo effects [8]. Because the benefits of vitamin C demonstrated in the Karlowski trial are consistent with those observed in other studies, the Karlowski trial should not be claimed as an example of placebo effect in action.

In 1984, Eby et al. reported that therapeutically administered zinc gluconate lozenges significantly shortened the duration of colds [3]. In this journal, Farr and Gwaltney proposed that the apparent benefit of zinc lozenges in the Eby trial may have resulted from the placebo effect, since the lozenges may have tasted bad [4]. However, Farr and Gwaltney provided no evidence that bad taste shortens the duration of colds. A dozen trials have examined the effect of zinc lozenges on the duration of the common cold [9]. Five studies with the lowest doses of zinc uniformly found no benefit, whereas three trials with high doses of zinc in the form of acetate found a 42% (95% CI 35% to 48%) reduction in the duration of colds and five studies with high doses of zinc in the form of other salts found a 20% (95% CI 12% to 28%) reduction. Depending on their composition, zinc gluconate lozenges can taste bad with time, whereas zinc acetate lozenges do not [10]. The most recent zinc acetate trial found no differences between zinc and placebo groups in bitter or bad taste or other adverse effects [11]. In their 1984 study, Eby et al. used a high dose of zinc gluconate, but the lozenges “were not bitter, rather they were chalky and bland in taste” [10, p.29]. Concluding from other studies with high doses of zinc as zinc lozenges [10], Eby's findings are attributable to high doses of zinc rather than the bad taste proposed by Farr and Gwaltney [4].

In an extensive Cochrane review that compared placebo arms with no-treatment arms, the authors concluded that they “did not find that placebo interventions have important clinical effects in general” [12]. Although the methodology of controlled trials is important, one should avoid exaggerating the role of blinding.

Presenting zinc lozenges and vitamin C for the common cold as examples of the placebo effect in action has two unfortunate consequences. First, readers mai understand falsely that there is more evidence for the clinical effects of placebo than there actually is. Second, readers may understand wrongly that the effects of zinc lozenges and vitamin C on the common cold are placebo effects.

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